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(54) Title: METHODS OF PROVIDING NEUROPROTECTION

(57) Abstract

Novel methods are disclosed for treating asymptomatic, acute and chronic neurological disease and attenuating further neuronal cell death in neurological diseases, employing a glycine site antagonist at the NMDA (N-methyl-D-aspartate) complex, e.g., 2-phenyl-1,3-propanediol dicarbamate (felbamate).

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# METHODS OF PROVIDING NEUROPROTECTION

## FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions which are antagonists at the glycine site on NMDA (N-methyl-D-aspartate) receptor complex, and to methods for the attenuation of acute or chronic neuronal damage in neurological disease ("neuroprotection").

## BACKGROUND OF THE INVENTION

Certain references cited below, which published in 1996, after the filing of the priority document, are not believed to represent prior art to the invention disclosed in the priority document (U.S. Serial No. 08/632,338), but are provided in order to simplify the explanation of the invention discussed herein.

The major excitatory neurotransmitter in the central nervous system is L-glutamate. The amino acids glutamate and aspartate cause convulsive activity when applied to the cerebral cortex (Hayashi, T., Jpn. J. Physiol., 3:46-64, 1952). Classification of the excitatory receptors include the AMPA, kainate and NMDA receptors (Watkins, J.C. Ann. Rev. Pharmacol. Toxicol., 21:165-204, 1981).

Unique features of the NMDA receptor-channel complex include: a sensitivity to blockade by physiological concentrations of $Mg^{++}$, a high permeability to $Ca^{++}$, and a requirement for coactivation by glycine. Thus, glycine and glutamate binding sites are allosterically coupled at the NMDA receptor complex. (Kemp, J.A., Trends Pharmacol Sci., 14(1):20-5, 1993).

Excitatory amino acid receptors are divided into NMDA and non-NMDA (kainate and AMPA) subtypes (Monaghan, D.T., Annu. Rev. Pharmacol. Toxicol., 29, 365-402, 1989). The NMDA receptor complex is located on the neuronal cell surface and is comprised of multiple

(i.e., glycine, polyamine, NMDA) binding sites as well as an ion-channel which has several internal binding sites. NMDA receptors are widely distributed in brain and spinal cord, with the highest densities in cerebral cortex and hippocampus (McBain, C.J., Physiol. Rev., 74:723-760, 1994, Leeson, P.D., J. Med. Chem., 37(24):4053 - 4067, 1994). The NMDA receptor has an important function in long-term potentiation (LTP) which is critical for the process of learning and memory (Cotman, C.W., Annu. Rev. Neurosci., 11:61-80, 1988).

The major excitatory neurotransmitter in the central nervous system is L-glutamate. Glutamate is the principal excitatory neurotransmitter in the brain and has an integral role in neurologic function including cognition, memory, movement and sensation. A recent review of neurological diseases has implicated a role for glutamate in the pathogenesis of multiple acute and chronic neurological disorders (Lipton, S.A., NEJM 330(9):613-622, 199). In both NMDA and non-NMDA classes of receptors, glutamate opens an ion channel which leads to a rapid influx of intracellular cations ($Na^+$ and $Ca^{++}$). Unique features of the NMDA receptor-channel complex include a strychnine insensitivity, blockade by physiological concentrations of $Mg^{++}$, a high permeability to $Ca^{++}$, and a requirement for coactivation by glycine. Thus, glycine and glutamate binding sites are allo-sterically coupled at the NMDA receptor complex, and glycine is required for activation of this receptor (Carter, A.J., Drugs Fut., 17(7):595-613, 1992, Leeson, P.D., J. Med. Chem., 37(24):4053-4067, 1994).

The amino acid glutamate causes convulsive activity (Hayashi, T., Jpn. J. Physiol., 3:46-64, 1952), produces cortical spreading depression (Van Harreveld, A., J. Neurochem., 3:300-315, 1959) and is elevated prior to complex partial seizures (During, M.J., Lancet, 341:1607-1610, 1993). Intracerebral administration of a glycine

agonist has been shown to increase the potency of NMDA in inducing seizures in mice (Singh, L., Eur. J. Pharmacol., 186:129-132, 1990).

Functional glycine antagonists can have either high intrinsic activity (D-cycloserine) or low intrinsic activity (HA-966). The compound HA-966 also displays weak partial agonist effects at the glycine site and bears the risk of proconvulsant activity (Wlaz, P., Eur. J. Neurosci, 6(11):1710-1719, 1994).

Felbamate (2-phenyl-1,3-propanediol dicarbamate) is a known pharmaceutical compound having been described in U.S. Pat. Nos. 2,884,444 (1959). Felbamate is a glycine site antagonist at the NMDA receptor.

U.S. patent 4,978,680 relates to the use of felbamate for the prevention and control of epileptic seizures. U.S. patent 5,082,861 relates to the use of felbamate for the prevention and control of epileptic seizures associated with complex partial seizures. U.S. patent 5,292,772 relates to the use of felbamate for the prevention and control of epileptic seizures associated with Lennox-Gastaut syndrome. U.S. patent 4,868,327 discloses a synthesis of felbamate.

Felbamate is a modulator of NMDA receptor function, and a glycine site antagonist (McCabe, R.T., J. Pharmacol. Exp. Ther., 264(3):1248-1252, 1993, Sofia,R.D., Ann. Neurol., 36(4):677-678, 1994, Wamsley, J.K., Exp. Neurol., 129(2):244-250, 1994, Taylor, L.A., Eur. J. Pharmacol., 289(2):229-233, 1995, White, H.S., Epilepsy Res., 20(1):41-48, 1995) but also has other reported mechanisms of actions (White, H.S., Epilepsia, 33(3):564-572, 1992, De Sarro, G., Eur. J. Pharmacol, 262(1-2):11-19, 1994, Serra, M., Eur. J. Pharmacol, 265(3):185-188, 1994, Rho, J.M., Ann. Neurol., 25:229-234, 1994, Subramanian, S., J. Pharmacol. Exp. Ther., 273:878-886, 1995). Felbamate does not cause the transient neuropathological changes seen in brain neurons after competitive antagonist administration (Olney, J.W., Arch. Gen. Psych., 52:998-1007, 1995).

Felbamate is protective against NMDA-induced convulsions in mice (White, H.S., Epilepsia 33(3):564-572, 1992; Sofia,R.D., Ann. Neurol., 36(4):677-678, 1994). 2-phenyl-1,3-propanediol dicarbamate showed efficacy in controlling partial seizures in epileptic patients (Wilensky, A.J., Epilepsia, 26(6); 602-606, 1985). The major anticonvulsant action of felbamate is due to interaction at the strychnine-insensitive glycine site at the NMDA complex (McCabe, R.T., J. Pharmacol. Exp. Ther., 264(3):1248-1252, 1993; White, H.S., Epilepsy Res., 20(1):41-48, 1995). In the rat hippocampal slice model of neural injury, felbamate provided excellent protection from glycine-induced injury, while 7-Cl-kynurenic acid (another glycine site antagonist) appeared to be toxic (Wallis, R.A., Brain Res., 685(1-2):115-125, 1995).

Felbamate has also been reported to interact at the AMPA/kainate receptor (De Sarro, G., Eur. J. Pharmacol., 262(1-2):11-19, 1994), facilitate the function of the GABA receptor (Serra, M., Eur. J. Pharmacol., 265(3):185-188, 1994, Rho, J.M., Ann. Neurol., 25:229-234, 1994), modulate $Na^+$ channel conductance (White, H.S., Epilepsia, 33(3):564-572, 1992), interact at the muscarinic and metabotropic receptors (Libri, V., J. Pharmacol. Exper. Ther., 277:1759-1769, 1996) and L-type (high-voltage-associated) calcium channels (Stefani, A.J., J. Pharmacol. Exper. Ther., 277:121-127, 1996). Felbamate decreased delayed neuronal cell death after kainic acid induced status epilepticus in animals (Chronopoulos, A., Epilepsia, 34(2):359-366, 1993). Glycine or d-serine were able to functionally reverse the anticonvulsant (Harmsworth, W.L., Epilepsia, 34(Suppl 2):92, 1993, Coffin, V., Eur. J. Pharmacol., 256:9-10, 1994) and ischemic protective effect (Wallis, R.A., Neuro. Report, 4:951-954, 1993) of felbamate. Conversely, other studies have not confirmed modulation of the GABA receptor (Ticku, M.K., Epilepsia, 32(3): 389-391, 1995), prevention of kainate-induced toxicity

(Kanthasamy, A.G., Brain Res 705:97-104, 1995), or glycine site antagonist mechanism of action (Rho, J.M., Ann. Neurol., 25:229-234, 1994, Subramanian, S., J. Pharmacol. Exp. Ther., 273:878-886, 1995).

In culture, antagonism of the glycine site or channel of the NMDA receptor prevents hypoxia-induced degeneration (Priestly, T., Brain Res., 531:183-8, 1990). In animal models of stroke (ischemia), felbamate was found to decrease neuronal death and delayed-ischemic necrosis when administered post-hoc (Wasterlain, C.G., Neurology, 43:2303-2310, 1993) and delayed apoptosis of the CA1 hippocampal granule cells (Wasterlain, C.G., Stroke, 27:1236-1240, 1996). Felbamate has been proposed as a therapeutic treatment for the prophylaxis of stroke in humans (Fisher, M., Stroke, 25(5):1075-1080, 1994).

Excessive NMDA receptor activation by excitatory amino acids or neurotoxic mediators of inflammation has been implicated in the pathogenesis of acute and chronic neurological diseases (Beal, M.F., FASEB J. 6:3338-3344, 1992). In acute neurological disorders, a sudden toxic elevation of glutamate may cause neuronal death by over-stimulation of the NMDA receptor. In chronic neurological disease, defective mitochondrial function or abnormal cellular metabolism may result in excitotoxic death by increasing the vulnerability of the neuronal cells to endogenous glutamate (Novelli, A., Brain Res., 451:205-212, 1988, Simpson, J.R., Exper. Neurol., 121:57-64,1993, Henneberry, R.L., Ann. NY. Acad. Sci., 568:225-233, 1989). Bioenergetic defects resulting in cellualr energy depletion would produce resting membrane depolarization and a subsequent removal of the Mg++ dependent NMDA receptor block. These events would produce neuronal susceptability to normally non-toxic effects of endogenous glutamate resulting in accumulation of intracellular calcium and delayed neuronal death (Cox, J.A., Brain Res., 499:267-272, 1989, Beal, M.F., Ann. Neurol., 31:119-130, 1992). Abnormal NMDA receptors

in disease states (either quantitatively or qualitatively) could also increase the probability of neuronal death by bioenergetic defects (Albin, R.L., Neurology 42:733-738, 1992). In a presymptomatic patient with Huntington's disease who came to necropsy, a reduction in the number of NMDA receptors was found in the basal ganglia suggesting that insidious receptor loss is involved in the pathophysiology of this disease (Albin, R.L., NEJM 322:1293-1298, 1990). Thus, the NMDA excitotoxic hypothesis may represent a final common pathway for neuronal death in acute and chronic neurological disease. Glycine-site NMDA antagonists such as felbamate, while not eliminating the cause of the the chronic neurological disease, will prolong the life-span of the neuronal cell undergoing chronic energy failure and also protect against delayed cellualr necrosis and apoptosis in acute neurological disorders.

**Felbamate and Adverse Events**

In clinical studies prior to FDA approval, felbamate was evaluated both as an "add-on" therapy in patients with intractable seizures i.e., in combination with other standard anti-epileptic drugs; and as monotherapy. There were several case reports of a decrease in platelets and other hematologic parameters but these were mild, reversible and occurred in combination with other antiepileptic drugs (i.e., valproic acid, carbamezepine) known to have these side effects. There were no reported cases of liver failure of bone marrow suppression prior to drug approval. The drug interaction of felbamate causes increases in the serum levels of dilantin, valproic acid, phenobarbitol, and the toxic epoxide metabolite of carbamezepine.

Felbamate was approved for use by the FDA in July 1993. In 1994 there were reports of felbamate causing aplastic anemia (Pennel, P.P., Neurology, 45:456-460, 1995) in 21 patients with 7 deaths, and

hepatic failure in 11 patients with 4 deaths (O'Neil, M.G., Neurology, 46:1457-1459, 1996). As a result, the FDA and the manufacturer sent a letter to all physicians in August 1994 requiring the withdrawal of felbamate from patients except in those cases in which the risk of seizure exceeded the risk of aplastic anemia. Warnings were added to the prescribing information and a blood test was required every two weeks. In a study published after the FDA warning (Li, L.M., Eur. Neurol., 36:146-148, 1996) one-hundred and eleven patients with refractory epilepsy were treated with adjunctive felbamate therapy. No cases of aplastic anemia or hepatic failure were observed when serum levels of anti-convulsant drugs were monitored. In addition, the safety of felbamate in a suicidal overdose was reported (Nagel, T.R., Ped. Emerg. Care., 11(6):369-371, 1995). An adolescent patient acutely consumed a total oral dose of 6900 mg and suffered no neurological, hematological or hepatic abnormalities.

Other reported adverse events include thromocytopenia (Ney, G.C., Neurology, 44:980-981, 1994), toxic epidermal necrolysis (Travagline, M.T., Pharmacotherapy, 15(2):260-4, 1995) anaphylaxis (O'Neil, M.G., Ann. Pharmacother., 29(4):430,1995) mania (Hill, R.R., Psychosomatics, 36(4):404-6, 1995) psychosis (Knable, M.B., J. Clin. Psychopharmacol., 15(4):292-3, 1995) and movement disorder (Kerrick, J.M., Neurology, 45(1):185-7 1995).

## OBJECTS OF THE INVENTION

One of the objects of the present invention is to provide compositions and methods for the treatment of acute and chronic neurological disorders that involve excessive activation of the NMDA receptor.

Another object of the present invention is to provide a method for attenuation of cell death caused by excessive activation

of the NMDA receptor by administering the drug prophylactically and chronically when the patient has asymptomatic or pre-clinical neurological disease.

Another object of the present invention is to provide compositions and methods effective to control or attenuate acute or chronic neurological disorders.

A further objective of the present invention is to provide compositions and methods for the prevention and control of acute or chronic neurological disorders that involve excessive activation of the NMDA receptor, which compositions are relatively non-toxic, have a high degree of effectiveness and continue to produce a therapeutic response over long periods of time.

A further object of the invention is to provide a method to visualize and quantitate NMDA receptors in vivo in normal human controls, asymptomatic and clinical disease states.

Still another object of the present invention is to provide a method for the attenuation of neuronal death caused by excessive activation of the NMDA receptor by elevated basal excitatory amino acid levels, seizures or status epilepticus.

Moreover, it is a further object of the present invention to provide methods for the attenuation and control of acute and chronic neurological disorders that involve excessive activation of the NMDA receptor.

## SUMMARY OF THE INVENTION

The subject invention relates to methods for treating acute and chronic neurological diseases and preventing neuronal cell death in neurological diseases, in mammals including humans, employing a glycine site antagonist at the NMDA receptor. The antagonists are administered intravenously or orally, acutely or chronically to attenuate further neuronal damage and death. Advantageously, the

drug is given prophylactically and chronically when the patient has asymptomatic or pre-clinical neurological disease.

The invention also relates to a method of determining NMDA receptor level in a mammal comprising administering labeled felbamate, and determining the amount of labelled felbamate which is bound to neurons.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to pharmaceutical compositions and to methods for the attenuation of acute and chronic neurological disorders that involve excessive activation of the NMDA receptor. Advantageously, the present invention relates to methods for neuroprotection in neurological disease(s) through the administration of therapeutic compositions, either intravenously or orally, which contain for example, as an active ingredient 2-phenyl-1,3-propanediol dicarbamate, commonly known as felbamate. The compound felbamate may be administered prophylacticall, acutely, subacutley or chronically, depending on the various neurolgical disease states. This compound has multiple mechanisms of action, of which one is a glycine site antagonist at the NMDA (N-methyl-D-aspartate) receptor.

NMDA receptor antagonists can be divided into noncompetitive (acting at the receptor channel complex) and competitive (acting at the NMDA recognition site) or modulatory sites (glycine, polyamine).

Although a competitive channel blocker can reduce damaging overstimulation of the excitatory portion of the receptor, it is also likely to eliminate the receptor's normal physiological functions. Thus, cognitive and memory brain functions are compromised and hence, most channel blockers cannot be administered safely to humans. In contrast, antagonists of receptor modulatory sites inhibit the toxic effects of high glutamate concentrations while sparing physiologic

functions of glutamate. Thus, modulatory antagonists such as a glycine site antagonist, can be safely administered to humans.

## COMPOUNDS OF THE INVENTION

Compounds of the invention include felbamate, quinoxalinediones including the ACEA compounds (1011, 1021, 1031, 1328), pyridazinoindole, ACPC (1-aminocyclopropane carboxylic acid), 1,4 dihydroquinoxaline-2,3-diones, 4-hydroxy-2-quinalones, 4-amino-2-carboxytetrahydroquinolines and trans-4-hydroxypipecolic acid-4-sulfate.

### In vivo NMDA Receptor Imaging

The subject invention provides a technique to image and thus quantitate the NMDA receptor complex in neurological diseases in vivo. By radioactively labelling a compound which binds the glycine site, e.g., felbamate, to produce $^{13}$ N-felbamate or $^{11}$C-felbamate, and administering the labelled compound to a patient by, e.g., positron-emission tomography (PET) scanning. This technique permits one to diagnose asymptomatic, preclinical individuals with a neurological disease involving glutamate and the NMDA receptor. In addition it identifies and assesses clinical efficacy of treatment. Synthesis of $^{14}$C-felbamate for autoradiographic distribution in animal brain has been described (Cornford, E.M., Epilepsia, 37(1):15-18, 1996).

In a study of post-mortem brain tissue from Huntington's disease, glycine-site binding of the NMDA receptor was decreased in the caudate nucleus (62%) and frontal cortex (20%) which reflects the ongoing disease process (Reynolds, G.P., J. Neurol. Sci., 25(2):46-49, 1994).

Radioactively labelled felbamate quantitates the NMDA receptors in pre-clinical asymptomatic patients. Radioactively labelled felbamate can be utilized to diagnose disease states prior

to their clinical expression when neuronal cell death has already significantly occurred (Albin, R.L., NEJM 322:1293-1298, 1990). In a variety of neurological diseases, symptoms do not occur until levels of NMDA receptors are greatly reduced. Diseases where this diagnostic technique is particularly useful include Parkinson's, Huntington's, Alzheimer's, Tourette's, adrenalleukodystrophy, CNS vasculitis, mitochondrial myopathies, HIV dementia, depression, ALS, movement disorders and Down's Syndrome.

## THERAPEUTIC USES OF THE COMPOUNDS OF THE INVENTION

Felbamate and other antagonist at the glycine site of the NMDA receptor are useful in the treatment of multiple neurologic diseases, in which inflammatory neurotxins and excitatory amino acids, of which at least glutamate is involved in the pathophysiology. ACEA compounds are administered at daily doses between 1-150 mg/kg, most advantageously between 20-40 mg/kg in each of the disorders discussed below.

**Prevention of Neuronal Degeneration and Brain Atrophy in Epilepsy**

Epilepsy, a disease which has been characterized as a paroxysmal, self-sustaining and self-limited cerebral dysrhythmia, genetic or acquired in origin and physiologic or organic in mechanism. Seizures which are evoked in an otherwise healthy brain by other factors (alcohol withdrawl, metabolic conditions, cocaine, etc.) are termed non-epileptic seizures. Epilepsy is usually classified, by clinical and electro-encephalographic observations, into four general classes:

1) Grand mal

2) Petit mal

3) Psychomotor (complex partial)

4) Autonomic

Those afflicted with epilepsy have one or a combination of the above seizure types.

Prior to the present invention, all drugs used in the treatment of epilepsy function as prophylactics against the symptoms of epilepsy, i.e., the reduction and control of epileptic seizures, rather than being prophylactics against the sequela of seizures, i.e., brain atrophy, cognitive dysfunction.

Although it is generally recognized that approximately 50% of epileptic patients can be controlled with presently available anti-epileptic medications, there is a continuing long felt need for more selective and less toxic anti-epileptic drugs. The desiratum of the art has been to provide a non-toxic, non-sedative, long-acting and highly effective anti-epileptic drug.

NMDA receptors play a significant role in epilepsy and seizures, particularly in the initiation and/or the propogation of epileptic dischages. Quantitative increases in the the number of NMDA and glycine receptors have been identified in a kindling model of complex partial epilepsy (Yeh, G.C., Proc. Natl. Acad. Sci., 86:8157-8160, 1989). Status epilepticus and seizures are known to be associated with a significantly greater future risk of recurring seizures (Falconer, M.A., Lancet, 2:767-770, 1974).

Elevated amino acid (i.e., glutamate, aspartate, glycine) content have been reported in neursugically removed epileptogenic focal epilepsy (Perry, T.L., Neurology, 31:872-876, 1981) and human epileptic cortex (Sherwin, A., Neurology, 38:920-923, 1988, Carlson, H., Neurosci. Lett., 140:30-32, 1992). In addition, both epileptic patients and first-degree relatives had elevated plasma glutamic acid levels suggesting a genetic basis for altered glutamate metabolism in epilepsy (Janjua, N.A., Epilepsy Res., 11:37-44, 1992).

There is considerable controversy as to whether epilptic activity is a cause or consequence of the neuronal damage (i.e., gliosis, atrophy, decrease number of dendritic spines) observed in brain tissue (Thompson, S.M., Brain Pathol., 3:413-419, 1993). It has been proposed that the excitotoxic effect of elevated levels of glutamate and aspartate prior to seizures are insufficient to cause neuronal loss (Meldrum, B.S., Brain Pathol., 3:405-412, 1993). In addition, it is not currently thought that neuronal loss accompanies brief individual siezures since no quantitative data from animal experiments show that a single brief seizure (less than five minutes duration) can cause neuronal cell loss (Meldrum, B.S., Brain Pathol., 3:405-412, 1993).

Glycine site antagonists have been shown to act as anticonvulsant agents (Croucher, M.J., Neurosci. Lett., 118:29-32, 1990, Croucher, M.J., Brain Res., 543:91-96, 1991) although glycine antagonists with low intrinsic efficacy have proconvulsant activity (Wlaz, P., Eur. J. Neurosci., 6(11):1710-1719, 1994). In convulsant-treated cultures, non-competitive NMDA antagonists were unable to reduce cell death (Thompson, SM., Brain Pathology, 3:413-419, 1993).

In a study of the etiology of complex partial seizures using microdialysis, elevated levels of glutamate occur prior to a complex partial seizure in humans (During, M.J., Lancet, 341:1607-1610, 1993). In addition, resting levels of glutamate were elevated in the temporal lobes in one-third of these patients.

We propose a novel hypothesis that congenital or eviromental abnormalities produce alterations in glutamate metabolsim and other amino acid metabolism. Both elevated resting glutamate levels and pre- and post epileptic elevations of glutamate cause acute but more commonly a chronic over-stimulation of the NMDA receptor. Prolonged chronic exposure may eventually cause metabolic or quantitative and qualitative abnormalities of the NMDA receptor resulting in delayed

neuronal cell death. The epileptic discharge, mediated by synaptically released glutamate, activates both NMDA and non-NMDA receptors which subsequently produce neuro-pathological effects by both acute and delayed chronic intracelluar calcium influx. The elevated levels of glutamate, both resting and prior to and after seizure activity, in patients with complex partial seizures is the etiology of brain atrophy (i.e., hippocampus) observed on brain MRI and necropsy.

According to the subject invention, patients with complex seizures are administered a glycine site NMDA antagonist such as felbamate, even if other drugs are effective for seizure control, to prevent neuronal degeneration and brain atrophy ("neuroprotection") by either acute or chronic mechanisms of NMDA receptor activation. The antagonist is administered to patients with seizure disorders to prevent future delayed cellular necrosis from elevated resting levels of glutamte, in the event that elevated glutamte episodes occur in the absence of a clinical seizure, or in the event that a seizure or status epilepticus occurs. The antagonist has a neuroprotective effect after status epilepticus, even when induced by mechanisms other than that of the NMDA receptor (Chronopoulos, A., Epilepsia, 34(2):359-366, 1993).

Felbamate administered to normal adults in doses of 3600 mg/day have resulted in trough serum levels of 83 + 21 µg/ml. Studies in a rat model of hypoxia-ischemia, which cause acute elevations of glutamte, suggest that felbamate 300 mg/kg decreassed the volume of infarction and delayed cellular necrosis (Wasterlain CG., Neurology 43:2303-2310, 1993), maximal at serum levels greater than 100 µg/ml, but that felbamate serum levels greater than 100 µg/ml were required for effective neuroprotection to prevent apoptosis (Wasterlain, C.G., Stroke 27:1236-1240, 1996). The current method of administering felbamate is to add it to existing drug

regimens as polytherapy. There is currently no recognized serum therapeutic range for felbamate. Due to drug interaction, this results in substantially lower serum felbamate levels in patients. In addition, although felbamate monotherapy has resulted in several isolated reports of serum levels greater than 100 µg/ml, no patient has been on felbamate monotherapy for at least one year, or sustained a serum level greater than 100 µg/ml for at least one year. We propose that serum felbamate levels of at least 100 µg/ml for a duration greater than one year is necessary for neuroprotection against both chronically elevated brain glutamate levels and acute, episodically elevated pre- and post-seizure glutamate levels.

Felbamate, administered chronically in oral doses of 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25-300 µg/ml), is efficacious in attenuating neuronal cell death from acute elevations of glutamate during seizures. More advantageously, serum levels ranging from 100-300 µg/ml, is efficacious in preventing delayed cell death, apoptosis, and atrophy in epilepsy when administered chronically for at least one year in duration.

**Sepsis**

In systemic blood infections, coma and cardiac/respiratory dysfunction can lead to death. Coma and neurological dysfunction occur after the administration of antibiotics, which are believed to increase the release of toxins as they kill bacteria. Elevated levels of quinolinic acid cause neuronal death by NMDA receptor over-stimulation. Toxins from the bacteria are believed to increase the production of cytokines and CSF-quinolinic acid (Heyes, M., Brain, 116:1425-1450, 1993) causing neurological symptoms and neuronal cell death by NMDA receptor over-stimulation.

A glycine site NMDA antagonist such as felbamate attenuates neurological morbidity and mortality in sepsis. Felbamate can be administered most advantageously by the intravenous route or chronically in oral doses at the time of diagnosis of sepsis and chronically in oral doses for six months or more after recovery. Felbamate, administered in oral doses of 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing neuronal cell death in sepsis.

**Meningitis**

Both viral and bacterial meningitis have been found to increase CSF-quinolinic acid levels (Heyes, M., Brain, 116:1425-1450, 1993) while the duration of excessive CSF-glutamate levles predict poor clinical outcome in patients with bacterial meningitis (Spranger, M., Arch. Neurol. 53:922-996, 1996). The neurological morbidity and mortality may be caused by excessive NMDA receptor stimulation. A glycine site NMDA antagonist prevents neurological morbidity and mortality in meningitis.

Felbamate can be administered most advantageously by the intravenous route or chronically in oral doses at the time of diagnosis of meningitis and chronically in oral doses for six months or more after recovery. Felbamate, administered in oral doses of 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing neuronal cell death in meningitis.

**Adrenoleukodystrophy**

Adrenoleukodystrophy (ADL) is an X-linked recessive disorder of myelin metabolism which causes seizures and dementia in young males. Pathologically, it has characteristics of an inflammatory

disorder, suggesting that cytokines and quinolinic acid are involved in its etiology. A glycine site NMDA antagonist has efficacy as an anticonvulsant as well as a neuroprotectant.

Felbamate, administered chronically in oral doses of 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing neuronal death and seizures in ADL.

**CNS Vasculitis**

CNS vasculitis, an inflammatory condition of the cerebral arteries, occurs in multiple autoimmune diseases (i.e., rheumatoid arthritis). Neurological sequela include stroke, seizures and dementia. Quinolinic acid has been found to be elevated and correlate with the degree of brain damage by MRI and clinical dementia.

A glycine site NMDA antagonist has efficacy in preventing the neurological the sequela of CNS vasculitis (stroke, seizure and dementia). Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing neuronal degeneration in CNS vasculitis.

**Impotence**

Penile erection is induced by the NMDA receptor activation of nitric oxide in the paraventricular nucleus of the hypothalamus (Melis, M.R., Neuro. Sci. Lett., 179:9-12, 1994). Epilepsy patients treated with felbamate, an antagonist at the glycine site of the NMDA receptor complex, reported an increase in libido. A common side effect of felbamate is increased mental energy and alertness.

A glycine site NMDA antagonist decreases primary and secondary impotence. Felbamate, administered chronically in oral

doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in increasing sexual libido.

**Schizophrenia**

Schizophrenia is a chronic psychotic disorder which is believed to be caused by a dopamine metabolic disorder. Genetic influences are involved and brain atrophy occurs both in schizophrenic patients and in their asymptomatic monozygotic twins. A glutamate hypothesis with NMDA involvement has been suggested to be also involved in the pathophysiology of schizophrenia (Olney, J.W., Arch. Gen. Psych., 52:998-1007, 1995). D-cycloserine, a partial agonist at the glycine site of the NMDA receptor, caused deterioration of the patient's psychotic symptoms in schizophrenia (Cascella, N.G., J. Neurol. Transm. Gen. Sect., 95(2):105-111, 1994).

A selective interaction between glutamate and dopaminergic mechanisms involving NMDA receptors in the limbic forebrain has been suggested by the ability of glycine site antagonists to selectively antagonize the stimulant effects of d-amphatamine on dopamine synthesis in rat nucleus accumbens but not in striatum (Hutson, P.H., Br. J. Pharmacol., 103:2037-2044, 1991). Haldol, a common treatment for schizophrenia, has properties of a partial agonist for the strychnine-insensitive glycine site on the NMDA receptor (Fletcher, E.J., Eur. J. Pharmacol., 235(2-3): 291-295, 1993).

Glycine site antagonists, including felbamate, function as "atypical neuroleptics" in the treatment of schizophrenia and other psychoses (Leeson, P.D., J. Med. Chem., 37(24):4053 -4067, 1994). A glycine site NMDA antagonist such as felbamate, is a treatment for glutamate induced atrophy in patients with schizophrenia. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25

µg - 300 µg/ml), is efficacious in preventing neuronal degeneration and brain atrophy in schizophrenia.

**Drug Addiction**

Symptoms of opiate withdrawal in drug addiction may be in part mediated by the NMDA receptor complex in the rostral medulla. Felbamate has been reported to attenuate the severity of naloxone precipitated withdrawl in a dose related manner in rats (Kosten, T.A., Neuropsychopharm., 13:323-333, 1995). A glycine site antagonist at the NMDA receptor with properties of oral or IV administration, good tolerability, and low adverse experience profile is a treatment for drug addiction, tolerance, dependency and withdrawal.

Felbamate can be administered most advantageously by the intravenous route or chronically in oral doses at the time of diagnosis of withdrawl symptoms and chronically in oral doses for six months or more after recovery. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing the autonomic and mental adverse experiences of drug addiction.

**Multiple Sclerosis**

A portion of the cortical brain damage that occurs in acute attack of multiple sclerosis (MS) and chronic progressive MS is due to an inflammatory upregulation of cytokines and quinolinic acid (Heyes, M., Brain, 116:1425-1450, 1993). Brain atrophy and cognitive dysfunction are common in MS.

A glycine site NMDA antagonist has efficacy in protecting cortical neurons ("neuroprotection") in MS. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day,

advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing neuronal degeneration in MS.

**Fatigue**

Fatigue is common in chronic diseases (i.e., multiple sclerosis, post-polio syndrome, Parkinson's) and in chronic fatigue syndrome. Chronic fatigue syndrome is believed to have a viral component in its etiology with involvement of cytokine up-regulation and potentially NMDA stimulation.

A glycine site NMDA antagonist provides symptomatic relief of fatigue as well as providing neuroprotection in the various disease states. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in treating fatigue of central nervous system etiology.

**Lead Poisoning**

Chronic or acute lead poisoning produces neuronal symptoms and brain damage by excessive stimulation of the NMDA receptor. Lead has been postulated to bind to the zinc binding site in the NMDA ion channel. Chronic treatment of rats with lead showed a slight increase in NMDA receptor density in the adult forebrain homogenates (Schulte, S., Neurotoxicology, 16(2):309-317, 1995).

A glycine site NMDA antagonist provides acute and prophylactic neuronal protection by controlling both NMDA function and quantity in these conditions. Felbamate can be administered most advantageously by the intravenous route or chronically in oral doses at the time of diagnosis of acute lead poisoning and chronically in oral doses for six months or more after recovery. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25

µg - 300 µg/ml), is efficacious in preventing neuronal degeneration from lead poisoning.

**Mitochondrial Dysfunction**

Mitochondrial dysfunctions are characterized by a mitochondrial abnormality (intracellular structures which produce energy for the cells) and other inherited or acquired biochemical disorders (Beal, M.F, Ann. Neurol. 31:119-130, 1992). Diseases or conditions include MELAS syndrome, MERF syndrome, Leber's disease, Wernicke's encephalopathy, Rett syndrome, homocystinuria, hyperprolinemia, nonketotic hyperglycinemia, hydroxybutyric aminoaciduria, sulfite oxidase deficiency, and combined systems disease (B12 deficiency).

A glycine site NMDA antagonist provides neuronal protection in these conditions. Felbamate can be administered most advantageously by the intravenous route or chronically in oral doses at the time of diagnosis and chronically in oral doses for six months or more after recovery. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious preventing neuronal degeneration in mitochondrial myopathies.

**HIV Dementia**

Patients who become HIV(+) have early pre-clinical brain neuronal deterioration as measured by NMR spectroscopy. When HIV(+) patients convert to AIDS, brain involvement produces dementia and is universally fatal. The mechanisms of brain deterioration appear to involve production of neurotoxic substances (i.e., quinolinic acid) that activate NMDA receptors and cause neuronal death by inducing intra cellular $Ca^{++}$ overload (Giulian, D., Science 250:1593-1596, 1990, Heyes, M.P., Ann. Neurol., 29:202-209, 1991a).

Blocking the NMDA receptor at the glycine site functions as neuroprotection and prevents neuronal death. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing neuronal degeneration in HIV dementia.

**Pain**

The centers of pain-transmitting structures in the spinal cord, thalamus and certain layers of the cerebral cortex contain NMDA receptors. Intractable tic douloureux (Chesire, W.P., Clin. J. Pain, 11:139-142, 1995), has been effectively treated with felbamate at doses of 1200-2400 mg/day. Conditions such as peripheral neuropathy, terminal cancer pain and failed back surgery which are intractable to current treatment modalities benefit from felbamate treatment. In the formalin injection animal pain model, glycine site antagonists (Millan, M.J., Neurosci. Lett., 178(1):139-143, 1994, Vaccarino, A.L., Brain Res., 615(2):331-334, 1993) decreased the late phase pain response. In a rat model of painful peripheral neuropathy, felbamate produced significant reductions in all measures of pain (Imamura, I., J. Pharm. Exp. The., 275(1):177-182, 1995). Specifically, the action of felbamate was antihyperalgesic and antiallodynic rather than analgesic.

Blocking the NMDA receptor at the glycine site prevents chronic pain transmission and gives symptomatic relief without producing central nervous system side effects. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in alleviating chronic pain.

**Depression**

Felbamate, a glycine site antagonist improves cognitive function and mood when administered to epileptic patients. Vegetative depression is characterized by low mood, excessive somnolence and obesity. Vegetative depression responds to a glycine antagonist by increasing mood, having a stimulatory effect and producing weight loss by NMDA mechanisms (Ketter, T.A., Epilpsey Res., 23(2):129-137, 1996). In addition, activation of the NMDA receptor, which are partly located on the serotinergic nerve terminal, elicits a release of cortical serotonin (Fink, K., Naumyn Schmiedebergs Arch. Pharmacol., 352(4):394-401, 1995) a major neurotransmitter in depression.

Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in treating vegetative depression.

**Amyotrophic Lateral Sclerosis**

Amyotrophic Lateral Sclerosis (ALS) is a progressive disease of the motor tracts of the brainstem and spinal cord which produces muscle weakness, wasting and death. Excessive glutamate stimulation may be involved in the pathogenesis of this disease (Rothstein, J.D., Ann. Neurol., 28:18-25, 1990). The number of NMDA receptors in the spinal cord is reduced in patients with ALS (Shaw, P.J., Brain Res., 637:297-302, 1994). Abnormal glycine and glutamate metabolism produce neurotoxicity by NMDA mechanisms (Virgo, L., Brain Res., 676:196-204, 1995).

A glycine site antagonist, which prevents these NMDA receptors from being excessively stimulated, prevents weakness and death in ALS. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day

(serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing ALS.

**Parkinson's Disease**

Parkinson's Disease (PD) is a selective degeneration of predominately $D_2$ dopaminergic neurons in the substantia nigra (motor portion of the basal ganglia) which produces progressive motor symptoms of rigidity and bradykinesia (slowness of movement). An NMDA-excitatory mechanism of early neuronal cell death is involved in the etiology of PD (Beal, M.F., Ann. Neurol., 31:119-130, 1992, Beal, M.F., FASEB J., 6:3338-3344, 1992). Felbamate has been shown to antagonize the $D_2$ (dopamine receptor) in an animal model of cataplexy (Kretchmer, B.D., Neurosci Lett., 179(1-2):115-118, 1994).

An NMDA glycine site antagonist which prevents NMDA receptors form being excessively stimulated, prevents progressive motor weakness and death (neuroprotection) in PD. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing neuronal death in PD.

**Attention Deficit Disorder**

Attention Deficit Disorder (ADD) is a brain disorder characterized impulsiveness, excessive motor symptoms and cognitive impairment. Current treatment includes the use of amphetamines which stimulate the brain. Felbamate monotherapy displayed stimulant-like effects in patients with epilepsy (Ketter, T.A., Epilpsey Res., 23(2):129-137, 1996). A glycine site NMDA antagonist has properties of cognitive enhancement and mental stimulation, without the side effects of dependency and decreased stature of amphetamines.

A glycine site NMDA antagonist is a useful treatment for ADD. Felbamate, administered chronically in oral doses ranging from 100-

15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in treating ADD.

**Narcolepsy**

Narcolepsy is a sleep disorder in which patients have an acute onset of REM (dreaming) sleep. A glycine site NMDA antagonist has properties of cognitive enhancement and mental stimulation.

A glycine site NMDA antagonist is a useful treatment for narcolepsy. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in treating narcolepsy.

**Alzheimer's Disease**

Alzheimer's Disease (DAT) is a progressive dementing illness which is caused by an abnormal form of amyloid deposition in the brain. Excessive amyloid deposition induces glutamate toxicity of the NMDA receptor (Koh, J-Y. Brain Res., 533:315-320, 1990, Mattson, M.P., J. of Neurosci., 12:376-388, 1992), resulting in neuronal death in areas of the brain that have a high density of NMDA receptors such as the hippocampus and cerebral cortex (areas of maximal neuronal death in DAT). The decrease in binding of NMDA receptors in DAT visual cortex correlated with increased numbers of neurofibrillary tangles. (Carlson, M.D., Neurobiol. Aging, 14(4): 343-352, 1993). Studies in animals have shown that glycine antagonist improve learning and attenuate scopalamine memory deficits (Fishkin, R.J., Behav. Neurol. Biol., 59(2):150-157, 1993, Finkelstein, J.E., Pharmacol. Biochem. Behav., 49(3):707-710, 1994, Baxter, M.G., Neurobiol. Aging, 15(2):207-213, 1994).

A glycine site NMDA antagonist with cognitive enhancement and neuronal protection properties is a useful treatment for DAT.

Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing neuronal degeneration in DAT.

**Childbirth**

All childbirth deliveries carry a risk of complications including premature labor, prolonged labor, hypoxia, etc. which place the fetus at risk for cerebral ischemic damage and cerebral palsy as well as the mother at risk for post-partum seizures, hypotension, hypoxia etc.

A glycine site NMDA antagonist with properties of excellent placental permeability, no teratogenesis and non-toxic properties to the fetus is a valuable prophylactic treatment to all mothers in labor. Felbamate is administered most advantageously intravenously or orally within 24 hours of expected normal delivery. In mothers with known pre-partum disorders, felbamate may be administered for several months prior to the expected date of delivery and chronically in oral doses for six months or greater after delivery. The infant may also be administered felbamate chronically in oral doses for six months or more. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing neuronal damage to both mother and infant in childbirth delivery.

**Surgical Anesthesia**

All patients who undergo general anesthesia for any surgical procedure are at risk for hypoxia, anoxia, cerebral embolism (i.e., fat, air), hypotension, hypoglycemia etc. which place the brain at risk for permanent damage.

A glycine site NMDA antagonist with neuronal protection properties is a useful prophylactic treatment in all anesthetized patients. Felbamate can be administered most advantageously intravenously or orally within minutes to 24 hours of surgery and chronically in oral doses for six months or more. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing neuronal damage during surgical anesthesia.

**Traumatic Head and Spinal Cord Injury**

In the rat SDH (acute subdural hematoma) model, both pre- and post treatment with a glycine site antagonist significantly reduced hemispheric ischemic damage (Tsuchida, E., J. Neurotrauma, 12(3):279-288, 1995). The role of NMDA receptors has been implicated in the etiology of traumatic brain injury (Faden, A.I., Science, 244:798-800, 1989) and contusive spinal cord injury (Wrathall, J.R., Brain Res., 586:140-143, 1992). Felbamate was shown to have a neuroprotective effect against CA1 hippocampal neurons in an animal model of traumatic head injury (Wallis, R.A., Eur. J. Pharmacol., 294:475-482, 1995). Patients with head and spinal cord injury have been found to have elevated cerebrospinal fluid levels of quinolinic acid which implicates the NMDA receptor in the etiology of neuronal cell death.

A glycine site NMDA antagonist with neuronal protection properties is a useful prophylactic treatment in all head and spinal cord injured patients by protecting against hypoxia and glutamate stimulation of the NMDA receptor. Felbamate can be administered most advantageously intravenously or orally within minutes of the diagnosis of traumatic brain or spinal cord injury and chronically in oral doses for six months or more. Felbamate, administered

chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing neuronal death in brain or spinal cord injury.

**Hypoglycemia**

Patients who suffer from an acute lowering of the blood sugar are at risk for cerebral brain damage by mechanisms involving the AMPA and NMDA receptor. Glutamate toxicity has been implicated in neuronal damage in hypoglycemia (Kaupinen, R.A., Neurosci., 27:175-182, 1988, Zeevalk, G.D., J. Pharmacol. Exp. Ther., 253:1285-1292, 1990).

A glycine site NMDA antagonist with neuronal protection properties is a useful prophylactic or acute treatment of hypoglycemia. Felbamate can be administered most advantageously intravenously or orally within minutes of the diagnosis of hypoglycemia and chronically in oral doses for six months or more. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing neuronal death in hypoglycemia.

**Tourette's Syndrome**

Tourette's syndrome is disorder of the basal ganglia which results in spontaneous movements and vocalizations. Damage to the basal ganglia may be due to glutamate or glutamate-like toxins mediated via the NMDA receptor.

A glycine site NMDA antagonist with neuronal protection properties is a useful treatment of Tourette's syndrome. Felbamate, administered chronically in oral doses ranging from 100-15,000

mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing neuronal death in Tourette's Syndrome.

**Hepatic Encephalopathy**

Hepatic encephalopathy is characterized by severe liver disease producing secondary neurological symptoms including seizures, cognitive dysfunction and extrapyramidal movements. NMDA receptors are involved in producing the latter three symptoms.

A glycine site NMDA antagonist with neuronal protection properties is a useful prophylactic treatment in all hepatic failure patients. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing neuronal death in treating seizures and neuronal degeneration in hepatic encephalopathy.

**Movement Disorders**

NMDA receptors are located in the subcortical areas of the brain which are involved in motor control. In a mouse model of posthypoxic myoclonus (a condition of hyperexcitability of the central nervous system), felbamate was found to have antimyoclonic properties. Felbamate has shown efficacy in control of tremor (Edwards, K.R., Neurology, 45:1951, 1995) and hemifacial spasm (Mellick, G.A., J. Pain and Symptom Management, 10:392-395, 1995) in humans at doses between 1800-2800 mg/day.

A glycine site antagonist is useful in the treatment of all movement disorders. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in

preventing neuronal death in treating movement disorders and preventing neuronal degeneration in movement disorders.

**Cognitive Enhancement in Normal Senescence**

Glutamate activation of the NMDA receptor has been postulated to be involved in the process of neuronal plasticity and long term memory (Monaghan, D.T., Annu. Rev. Pharmacol. Toxicol., 29:365-402, 1989). Age-related decreases in strychnine-insensitive glycine binding which may be associated with impairments of learning and memory which occur in aging animals (Miyoshi, R., Synapse, 6:338-343, 1990). Behavioral effects of felbamate in Lennox-Gastaut Syndrome revealed significant improvements in intellectual and motor functioning, attention and concentration, and memory (Gay, P.E., Psych. Rep., 77(3):1208-1210, 1995) which are consistant with cognitive enhancement.

A glycine site NMDA antagonist, such as felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing a decrease in cognitive function with normal aging.

**Down's Syndrome (Trisomy 21)**

Down's syndrome is a chromosomal syndrome with a frequency of 1 in 700 births. Mild retardation is universal and Alzheimer's disease, with neurofibrillary tangles and neuritic plaques, develop after the 40th year of life.

A glycine site NMDA antagonist such as felbamate, increases cognitive capabilities and can prevent the onset of Alzheimer's disease in Down's syndrome. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200

mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing neuronal degeneration in Down's Syndrome.

**Electroshock Therapy (ECT)**

Patients who undergo ECT may suffer cognitive complications including memory loss. Since ECT is an artificially induced seizure, neuronal damage is similar to that of chronic seizures. A mechanism of cognitive dysfunction is damage to the NMDA receptors of the hippocampus and cerebral cortex. ECT has been shown to increase the turnover of NMDA receptors in animals.

A glycine antagonist such as felbamate prevents NMDA induced neuronal damage from ECT treatment. Felbamate is administered most advantageously intravenously or orally prior to the administration of ECT and chronically in oral doses for six months or more. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing neuronal damage and delayed cellular necrosis as a consequence of ECT therapy.

**Brain Tumors**

Brain tumors produce elevated levels of quinolinic acid (Heyes, M., J. Neurol. Sci., 133:112-118,1995) which produce seizures, neuronal degeneration and brain atrophy.

A glycine site antagonist such as felbamate, administered chronically in oral doses of 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing seizures, neuronal degeneration and brain atrophy from brain tumors.

**Cerebellar Degeneration**

Cerebellar NMDA receptors have a different pattern of modulation at glutamate and glyucine sites compared to the forebrain. Thus, glycine plays a more critical role in the control of cerebellar NMDA function (Widdowson, P.S., J. Neurochem., 64(2):651-61, 1995). Atrophy is common in cerebellar degeneration.

A glycine site antagonist such as felbamate, administered chronically in oral doses of 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing cerebellar degeneration.

Having now fully described this invention it will be appreciated by those skilled in the art that the same can be performed within a wide range of equivalent parameters of composition, conditions, and modes of administration without departing from the spirit or scope of the invention or any embodiment thereof.

**WHAT IS CLAIMED IS:**

1. A method of protecting neuronal cells in a mammal having an acute or chronic neurological condition comprising administering a neuronal cell protecting amount of an antagonist of the glycine site of the NMDA receptor complex, to said mammal.

2. A method as in claim 1 wherein said chronic neurological condition is selected from the group consisting of: epilepsy, ADL, CNS vasculitis, impotence, schizophrenia, MS, fatigue, chronic lead poisoning, mitochondrial myopathies, HIV dementia, pain, depression, ALS, ADD, Parkinson's Disease, narcolepsy, Alzheimer's disease, drug addiction, Tourette's Syndrome, hepatic encephalopathy, movement disorders, Down's Syndrome, brain tumors and cerebellar degeneration.

3. A method as in claim 1 wherein said acute neurological condition is selected from the group consisting of: sepsis, meningitis, acute lead poisoning, hypoglycemia, childbirth, surgical anesthesia, and ECT.

4. A method as in claim 1 wherein said antagonist is selected from the group consisting of felbamate, quinoxalinediones including ACEA compounds (1011, 1021, 1031, 1328), pyridazinoindole, ACPC (1-aminocyclopropane carboxylic acid), 1,4 dihydroquinoxaline-2,3-diones, 4-hydroxy-2-quinalones, 4-amino-2-carboxytetrahydroquinolines and trans-4-hydroxypipecolic acid-4-sulfate.

5. A method as in claim 1 wherein said antagonist is felbamate.

6. A method as in claim 1 wherein said felbamate is administered intravenously.

7. A method as in claim 1 wherein said felbamate is administered orally or rectally.

8. A method for attenuation of cell death caused by excessive activation of the NMDA receptor by administering the drug

prophylactically and chronically when the patient has asymptomatic or pre-clinical neurological disease.

9. A method of determining NMDA receptor level in a mammal comprising

administering to said mammal labeled felbamate,

determining the amount of labeled felbamate which is bound to neurons in said mammal,

comparing the amount of labeled felbamate in normal control patients and in pre-clinical or clinical disease states.

10. A method as in claim 8 wherein said felbamate is radioactively labeled.

11. A method as in claim 9 wherein said determining step is subjecting said mammal to a PET (positron emission tomography) scan.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/05860

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) : A61K 31/24
US CL : 514/534
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/534, 541

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 4,978,680 A ( SOFIA ) 18 December 1990, claim 1. | 1, 2, 4-8 |
| X | US 5,292,772 A ( SOFIA ) 08 March 1994, claim 1 | 1, 2, 4-8 |
| Y | CARTER, A. J. Glycine antagonists : regulation of the NMDA receptor-channel complex by the strychnine-insensitive glycine site.DRUGS OF THE FUTURE. 1992, Vol. 17, No,7. pages 595-613, especially pages 605-607. | 1-8 |
| Y | LEESON, P. D.et al. The glycine site on the NMDA receptor: Structure-activity relationships and therapeutic potential. 25 November 1994, Vol. 37,No.24. especially pages 4060-4061. | 1-8 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search
24 JUNE 1997

Date of mailing of the international search report
11 AUG 1997

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Form PCT/ISA/210 (second sheet)(July 1992)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/05860

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-8

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/05860

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

Group I, claims 1-8, drawn to a method of treating an acute or chronic neurological condition, classifiable in class 514, subclass 534.

Group II, claims 9-11, drawn to a method of determining NMDA receptor levels, classifiable in class 560, subclass 164.

The inventions listed as Groups I and II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The inventions listed as groups I and II are a combination of different categories of claims; see PCT Administrative Instructions Annex B Part I (e).

**PCT** WORLD INTELLECTUAL PROPERTY ORGANIZATION
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(54) Title: METHODS OF PROVIDING NEUROPROTECTION

(57) Abstract

Novel methods are disclosed for treating asymptomatic, acute and chronic neurological disease and attenuating further neuronal cell death in neurological diseases, employing a glycine site antagonist at the NMDA (N-methyl-D-aspartate) complex, e.g., 2-phenyl-1,3-propanediol dicarbamate (felbamate).

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AMENDED CLAIMS
[received by the International Bureau on 8 October 1997 (08.10.97);
original claims 1-11 replaced by new claims 1-4 (2 pages)]

1. A method of treating sepsis and preventing neuronal degeneration and cell death in a human having sepsis, the method comprising the steps of:

administering to the human having sepsis a neuronal cell protecting antagonist of the glycine site of the NMDA receptor complex, wherein said antagonist is 2-phenyl-1,3-propandeiol dicarbamate at a serum level ranging from 25-300 ug/ml, in order to significantly attenuate neurological morbidity by preventing excessive stimulation of the NDMA receptor.

2. A method of treating HIV dementia and preventing neuronal degeneration comprising the steps of:

administering to a human having HIV dementia a neuronal cell protecting antagonist of the glycine site of the NDMA receptor complex, said antagonist being 2-phenyl-1,3-propoandeiol dicarbamate at a serum level ranging from 25-300 ug/ml, in order to attenuate neurological morbidity by preventing excessive stimulation of the NMDA receptor in the human having HIV dementia.

3. A method of treating meningitis comprising the steps of:

chronically administering to a human having meningitis a neuronal cell antagonist of the glycine site of

the NMDA receptor complex, wherein said antagonist is felbamate at a serum level ranging from about 25-300 ug/ml.

4. A method of treating CNS vasculitis and preventing neuronal degeneration and cell death in a human having CNS vasculitis, the method comprising the steps of:

administering to the human having CNS vasculitis neuronal cell protecting antagonist of the glycine site of the NMDA receptor complex, wherein said antagonist is 2-phenyl-1,3-propandeiol dicarbamate at a serum level ranging from 25-300 ug/ml, in order to significantly attenuate neurological morbidity by preventing excessive stimulation of the NDMA receptor.

## STATEMENT UNDER ARTICLE 19

This Amendment is submitted in order to bring the claims in the international application into conformity with those that have been allowed in the corresponding United States application. New claims 1-4 replaces all claims previously submitted.